

Dipyridamole combined with exercise for thallium-201 myocardial imaging

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SUMMARY A new stress test for thallium-201 myocardial imaging in which pharmacological coronary vasodilatation with dipyridamole is combined with dynamic exercise is described. In 38 patients with coronary artery disease the sensitivity, total number of defects, degree of redistribution, and visual quality of thallium-201 imaging were greater after dipyridamole with exercise testing than after exercise alone. When the data from these 38 patients were combined with the results of dipyridamole-exercise imaging in 49 patients in whom exercise electrocardiography had been inconclusive then the technique gave a sensitivity for coronary disease of 87% and a specificity of 92%. Dipyridamole also increased the sensitivity of the exercise electrocardiogram, so that no patient with coronary disease had a strictly negative dipyridamole-exercise stress test. Only five of 214 patients who have now undergone this test have had complications requiring reversal of vasodilatation with aminophylline. The combined use of dipyridamole and exercise in this simple technique is a reliable and safe improvement on standard thallium-201 imaging tests.

Thallium-201 myocardial imaging is now an established technique for the diagnosis of coronary artery disease.^{1,2} Although thallium-201 scintigraphy performed after maximal exercise (exercise imaging) may possess greater sensitivity for coronary disease than does exercise electrocardiography,^{3,4} false negative scintigrams are still found in about 25% of patients.⁵⁻⁷ While computer assisted quantitation of scintigrams is said to give greater sensitivity than simple visual analysis,^{8,9} falsely negative results can still be expected when the stress imposed before thallium-201 injection is insufficient to produce regional differences in thallium-201 distribution.

The two widely used stress methods for thallium-201 imaging are dynamic exercise and pharmacological coronary vasodilatation with dipyridamole.¹⁰ The purpose of these studies was to evaluate a simple technique in which maximal exercise testing is performed in the presence of a high plasma concentration of dipyridamole (a dipyridamole-exercise stress test). Studies of three groups of patients are described: in section 1 the sensitivity and quality of thallium-201 images obtained

with the new method were compared with standard exercise imaging. The overall sensitivity and specificity of dipyridamole-exercise imaging were assessed in section 2, and in section 3 the optimal time for exercise testing after the large oral dose of dipyridamole was determined by serial measurement of plasma concentrations.

Section 1: a comparison of dipyridamole-exercise imaging with standard thallium-201 imaging in patients with coronary artery disease

PATIENTS AND METHODS

Thirty eight patients with stable mild or moderate angina pectoris were studied (35 male and three female; aged between 38 and 62 years, mean 50.5 years). The selection criteria were as follows: (a) no electrocardiographic or angiographic evidence of previous myocardial infarction; (b) no myocardial ischaemia (angina or ischaemic ST segment changes) during the first six minutes of a treadmill exercise test (modified Bruce protocol); (c) unequivocal evidence of coronary artery disease. Important lesions had been demonstrated in all 32 patients who had undergone coronary arteriography. The remaining six patients were middle aged men with typical angina and an ischaemic ST

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segment response during exercise, who may therefore be assumed to have had coronary disease^{11 12} but whose symptoms did not warrant arteriography.

These criteria were designed to select those patients in whom standard thallium-201 imaging could be expected to show a relatively low sensitivity for coronary disease.^{3 13} By excluding patients with easily induced myocardial ischaemia the probability of angina being produced by dipyridamole alone was also reduced (unpublished observations).

Each patient gave informed consent to undergo exercise thallium-201 imaging on two separate occasions with a two week interval between tests. On one occasion, selected at random, exercise testing was preceded by the administration of dipyridamole as described below. On both occasions patients exercised to a symptom-limited end point and thallium-201 (2 mCi) was injected intravenously 45 seconds before exercise was stopped.

Protocol for dipyridamole-exercise testing

At least two hours after a light breakfast the patient took 300 mg of dipyridamole (three 100 mg capsules of Persantin, Boehringer-Ingelheim) by mouth, having been informed that this unusually large dose might cause headache, mild chest discomfort, or a feeling of warmth. Forty five minutes later any symptoms were recorded, a modified 12 lead electrocardiogram was analysed, and a 19 gauge butterfly cannula was inserted into a dorsal hand vein. In the absence of severe angina or ST segment changes the patient started treadmill exercise approximately 60 minutes after dipyridamole. When severe angina or ST segment changes were produced by dipyridamole alone thallium-201 was injected at rest and this was followed immediately by a slow intravenous injection of aminophylline (125–250 mg). Thallium-201 imaging was then performed without exercise.

Thallium-201 imaging

Early thallium-201 images were recorded within 20 minutes of stress testing and late images four hours after testing by means of an IGE Maxicamera 400T gamma camera with a high resolution converging

collimator. Planar images were obtained in the anterior, 45° left anterior oblique, and 60° left anterior oblique projections. A total of 400 000 events was collected for each image. The data were collected and processed by a Link Systems Dyanne computer. Five discrete regions of the left ventricular myocardium—anterolateral, apical, septal, inferior, and posterolateral—were defined. Each complete series of thallium-201 images (early and late) was inspected blindly and independently by three experienced observers. The images were analysed visually with and without smoothing, and in the first instance without contrast adjustment. It was agreed beforehand that any left ventricular region in which thallium-201 activity was at any point less than 75% of the maximum pixel value in the myocardial image should be classified as abnormal. Any disagreements were resolved by combined viewing of the images; after discussion the final judgment of the radiologist (RPHW) was accepted. Myocardial to background ratios were calculated for each set of images from the early 45° left anterior oblique projection. The region showing the highest activity was compared with a background (that is, pulmonary) region that was 2 cm directly above the superior cardiac border on the computer display.

Coronary arteriography

Coronary stenoses shown by selective arteriography were defined as being "important" when they produced a 90% loss of cross sectional area (equivalent to a 67% diameter loss) in a major artery. Lesions producing 50–89% cross sectional area loss were defined as "minor" and of doubtful importance; and vessels with 0–49% loss were defined as "normal".

Statistical analysis was performed by Student's paired *t* test.

RESULTS

In 80% of cases there was complete agreement between observers. The results of thallium-201 imaging after dipyridamole-exercise stress or exercise alone are summarised in Table 1. Twenty eight patients showed regional abnormalities on both occasions, whereas six showed abnormalities only after

Table 1 Results of thallium-201 imaging after dipyridamole-exercise or exercise testing in 38 patients with coronary disease

Result	Dipyridamole-exercise	Exercise
Patients with abnormal scintigrams	34/38 (89%)	29/38 (76%)
Total number of early defects	74	56
Total number of late defects	20	28
Percentage of defects showing redistribution	73	50
Myocardial to background ratio (mean (SD))	3.44 (0.57)*	2.99 (0.51)*

**p* < 0.01.

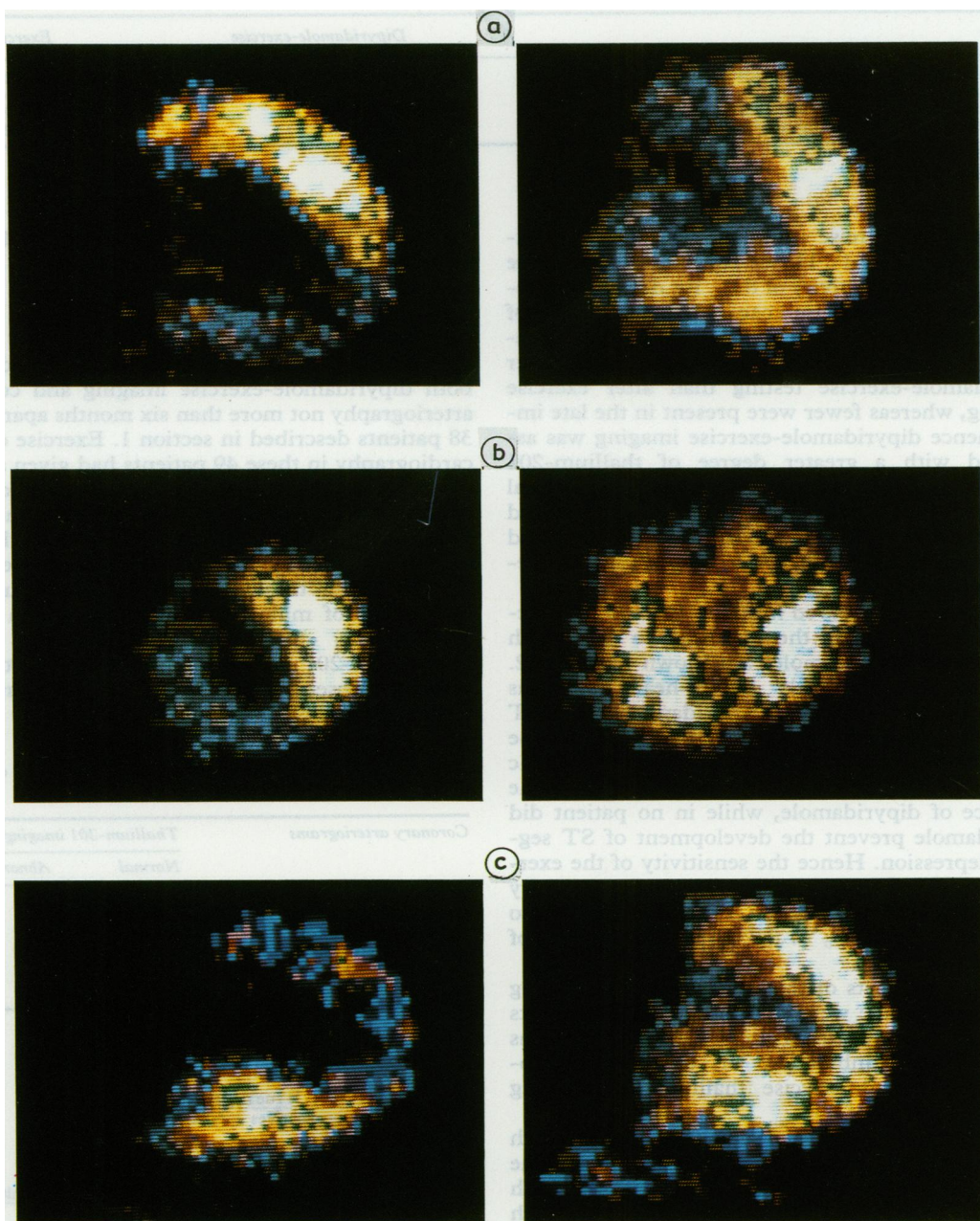


Fig. 1 Early thallium-201 images of three patients with coronary disease in whom dipyridamole-exercise imaging (left) showed abnormal regions whereas exercise imaging (right) did not. (a) Patient 1 (right coronary occlusion): inferior defect shown in anterior projection. (b) Patient 2 (right coronary occlusion, dominant vessel) inferior and septal defects in 45° left anterior oblique projection. (c) Patient 3 (left anterior descending stenosis) anterolateral defect in anterior projection.

Table 2 Changes in heart rate and electrocardiogram during exercise testing (with and without dipyridamole) in 38 patients with coronary disease

Variable	Dipyridamole-exercise	Exercise
Maximum heart rate (beats per minute) (mean (SD))	119 (22)*	126 (23)*
Maximum ST segment depression (mm) (mean (SD))	1.7 (1.0)	1.7 (1.0)
Patients showing > 1 mm ST segment depression	32/38 (84%)	29/38 (76%)
Combined sensitivity of thallium-201 and ECG	38/38 (100%)	36/38 (95%)

* $p < 0.05$.

ECG, electrocardiogram.

dipyridamole-exercise stress and one only after exercise stress (Fig. 1). Hence dipyridamole-exercise imaging had a sensitivity of 89% for detecting coronary disease and exercise imaging had a sensitivity of 76%. Considerably more abnormal regions were detected in the early images of the whole group after dipyridamole-exercise testing than after exercise imaging, whereas fewer were present in the late images; hence dipyridamole-exercise imaging was associated with a greater degree of thallium-201 redistribution than was exercise imaging. The visual quality of the thallium-201 images, as assessed quantitatively by their myocardial to background ratios, was significantly better after dipyridamole-exercise testing.

The changes observed in heart rate and the electrocardiogram during the two exercise tests (with and without dipyridamole) are shown in Table 2. Although a significantly lower heart rate was achieved in the presence of dipyridamole, mean ST segment depression was the same as after exercise alone. Three patients who did not show ischaemic ST depression during exercise alone did so in the presence of dipyridamole, while in no patient did dipyridamole prevent the development of ST segment depression. Hence the sensitivity of the exercise electrocardiogram for demonstrating coronary disease by ST segment depression was also increased—from 76% to 84%—by the addition of dipyridamole.

When the results of thallium-201 stress imaging with dipyridamole were combined with the results of exercise electrocardiography the sensitivity was 100%. The combination of exercise electrocardiography and exercise thallium-201 imaging gave a sensitivity of 95%.

Two patients developed persistent angina with ST segment depression after dipyridamole alone and so did not proceed to the exercise phase. Both were given intravenous aminophylline, and both showed two regional abnormalities on early imaging with redistribution at four hours. Three other patients experienced mild short lived angina without ST segment depression after dipyridamole and were able to proceed to the exercise phase.

Section 2: determination of the sensitivity and specificity of dipyridamole-exercise thallium-201 imaging

PATIENTS AND METHODS

We added a further 49 patients who had undergone both dipyridamole-exercise imaging and coronary arteriography not more than six months apart to the 38 patients described in section 1. Exercise electrocardiography in these 49 patients had given a result which was either indeterminate or which had conflicted with the patient's history. All these patients met the first two selection criteria outlined in section 1 and had undergone dipyridamole-exercise imaging either to aid diagnosis or to evaluate the importance of minor coronary stenoses on angiography.

Thallium-201 images were analysed by two experienced observers (PRW and RPHW) using the method described in section 1.

Table 3 Results of dipyridamole-exercise imaging and coronary arteriography in 87 patients

Coronary arteriograms	Thallium-201 imaging	
	Normal	Abnormal
Coronary disease demonstrated or presumed (n = 57)	7	50
Coronary disease not demonstrated (n = 25)	23	2
Minor coronary lesion present (n = 5)	3	2

$$\text{Sensitivity} = \frac{\text{True positives}}{\text{true positives} + \text{false negatives}} \times 100$$

$$= \frac{50}{50 + 7} \times 100 = 87\%$$

$$\text{Specificity} = \frac{\text{True negatives}}{\text{true negatives} + \text{false positives}} \times 100$$

$$= \frac{23}{23 + 2} \times 100 = 92\%$$

$$\text{Predictive accuracy of a positive result} = \frac{\text{Number of diseased patients with positive result}}{\text{all patients with positive result}} \times 100$$

$$= \frac{50}{52} \times 100 = 96\%$$

$$\text{Predictive accuracy of a negative result} = \frac{\text{Number of disease-free patients with a negative result}}{\text{all patients with a negative result}} \times 100$$

$$= \frac{23}{30} \times 100 = 76\%$$

RESULTS

The scintigraphic and angiographic findings are summarised in Table 3, with calculations of sensitivity, specificity, and predictive accuracy. Two patients with no coronary disease had a false positive scintigram—one had severe mitral regurgitation and gross electrocardiographic abnormalities, while in the other patient, who was shown to have a mild dilated cardiomyopathy, no dipyridamole could be detected in the plasma; hence it may be assumed that standard exercise imaging would also have produced a positive result in this patient. The five patients with coronary lesions of doubtful importance were excluded from the calculations.

Section 3: determination of optimal interval from dipyridamole to exercise testing—measurement of plasma concentrations

Sixteen patients undergoing dipyridamole-exercise testing agreed to serial venous blood sampling via an indwelling cannula at the times shown in Fig. 2. In one patient no dipyridamole could be detected in any sample and his results were excluded.

Mean dipyridamole concentration reached a peak 60 minutes after ingestion, although values that were almost as high were measured at 40, 80, 100, and 120 minutes after. At 300 minutes (when the redistribution images were being recorded) the mean concentration had fallen to 26% of the peak value.

Individually, 11 patients showed evidence of rapid absorption, whereas in three patients absorption was apparently much slower with peak values not being reached until after 120 minutes (Fig. 3).

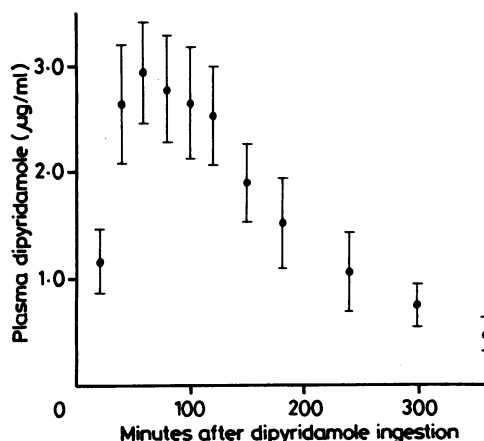


Fig. 2 Rate of clearance of 300 mg dipyridamole in 15 patients. Values are mean (SEM).

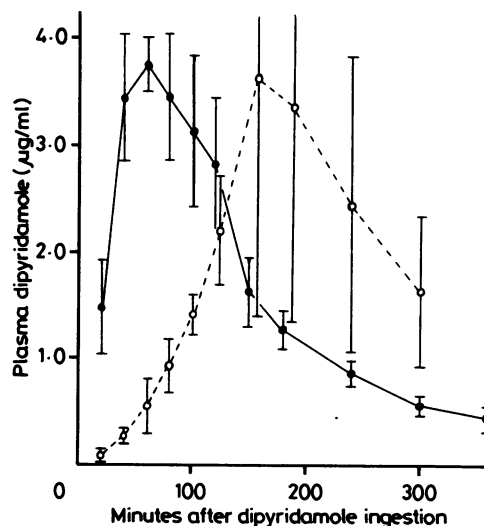


Fig. 3 Rate of clearance of dipyridamole in 11 early absorbers (●—●) and three late absorbers (○---○). Values are mean (SEM).

One patient (not included in Fig. 3) apparently absorbed very little dipyridamole, since his peak plasma concentration was only 0.69 µg per ml.

Discussion

RATIONALE OF DIPYRIDAMOLE-EXERCISE TESTING

These studies have demonstrated that pharmacological coronary vasodilatation with dipyridamole superimposed on exercise stress can result in an abnormal scintigram in patients with false negative scintigrams after exercise alone. Two actions of dipyridamole may be responsible. Firstly, dipyridamole is a potent coronary arterial dilator that acts selectively on the coronary resistance bed.¹⁴ When injected intravenously at maximal exercise, dipyridamole produces an increase in coronary flow greater than that produced by exercise alone.¹⁵ Intravenous dipyridamole combined with isometric handgrip exercise produces a greater increase in coronary flow than does either type of intervention alone, with the levels of flow (3.3 times the baseline values) exceeding any previously reported for the human coronary circulation.¹⁶ Since dynamic exercise is associated with a greater increase in coronary flow than is isometric exercise¹⁷ it is probable that dipyridamole-exercise stress increases coronary flow to an equal or even greater degree than dipyridamole combined with isometric handgrip.

The amount of thallium-201 entering myocardial

cells is determined not only by coronary flow but also by how much dipyridamole is extracted—that is the extraction fraction.¹⁸ When coronary flow is increased out of proportion to oxygen consumption, as occurs during dipyridamole induced vasodilatation,^{16,18} the extraction fraction falls. Dynamic exercise on the other hand increases oxygen consumption and hence thallium-201 extraction; however, in regions in which myocardial ischaemia occurs the ability to extract thallium-201 is reduced.¹⁸ In the present studies as in others^{13,19} dipyridamole infrequently caused myocardial ischaemia; in contrast exercise consistently produced angina or ST segment depression or both. In theory the combined stress of dipyridamole and exercise should therefore maximise regional differences in thallium-201 distribution in patients with coronary disease by the differing effects of both interventions on the delivery and extraction of the radionuclide.

A second property of dipyridamole is its undisputed ability to produce myocardial ischaemia in patients with coronary disease.^{19–21} Although patients with easily induced myocardial ischaemia were excluded from the present study, two patients developed angina after dipyridamole which was severe enough to require reversal by aminophylline. Five other patients either experienced mild angina after dipyridamole or demonstrated evidence of ischaemia considerably earlier in their exercise test. Two mechanisms may be responsible for the production of ischaemia: firstly, perfusion of the sub-endocardium may fall when flow across a stenosis of the nutrient artery is increased by, for example, vasodilatation.²² Secondly, dilatation of resistance vessels in well perfused regions may produce steal from regions which are dependent on a collateral circulation.^{23,24} There were 11 patients in whom dipyridamole undoubtedly produced myocardial ischaemia or was essential for the production of an abnormal scintigram; four of seven in whom angiography was performed were shown to have collateral dependent regions of viable myocardium.

The extent to which each of these two properties of dipyridamole was responsible for the improved sensitivity of dipyridamole-exercise imaging is uncertain. If, as seems probable, thallium-201 uptake by the lungs is not significantly affected by dipyridamole,²⁰ then the increased myocardial to background ratio observed with dipyridamole-exercise testing, which was responsible for the improved visual quality of the images, may be presumed to result primarily from increased myocardial blood flow. The finding that in four of the six patients in whom only dipyridamole-exercise imaging was abnormal the myocardial to background ratio was not enhanced suggests, however, that the pro-

duction of ischaemia by dipyridamole must also play an important role.

SENSITIVITY AND SPECIFICITY OF THALLIUM-201 IMAGING

The overall sensitivity for coronary disease of dipyridamole-exercise scintigraphy (the true-positive rate) was 87%; this was 13% better than the sensitivity of the standard exercise imaging. Others have reported a sensitivity of between 67%¹⁹ and 95%⁸ with exercise imaging and of between 67%¹⁹ and 93%²⁵ with intravenous dipyridamole imaging. The overall sensitivity of exercise imaging was 82% in 1077 patients who had this test from 1976 to 1979²⁶; however, these patients were unselected as regards disease severity, and many had previous myocardial infarction. Patient characteristics which tend to increase the sensitivity of thallium-201 imaging include previous myocardial infarction,²⁷ impaired left ventricular function,¹³ severe coronary disease,^{3,7} and an ineffective collateral circulation²⁸; while the method of image interpretation (visual or quantitative) and the criteria used to define abnormality are also important determinants of sensitivity. In the present studies patients with previous infarction, poor left ventricular function, and severe coronary disease—the correlate of an early positive exercise test²⁹—were excluded; while the criterion for abnormality (that is a $\geq 25\%$ deficiency of thallium-201 activity) was relatively strict and the method of interpretation was visual. Hence in a less carefully selected population and using a more refined method of interpretation an even higher sensitivity could no doubt have been achieved. It should be stressed, however, that any figure quoted for the sensitivity of a test is meaningful only when derived by studying the population in which the test will find clinical application—that is in symptomatic patients with conflicting or indeterminate exercise electrocardiograms.^{3,5,6}

Dipyridamole-exercise imaging achieved a specificity (true-negative rate) of 92% in 25 patients without important coronary disease. False positive results, of which there were two, occurred only in patients with other cardiac lesions who were therefore likely to show scintigraphic abnormalities.³⁰ No patient with a normal heart had an abnormal scintigram. In the cumulative data referred to above²⁶ the overall specificity of exercise thallium-201 imaging in symptomatic patients was 90%. In individual studies the estimates of specificity, which have ranged from 67%¹³ to 100%,³ have often been based upon very small patient numbers. As with test sensitivity, patient selection is all important in the determination of specificity. The present study also shows that the inclusion of subjects who have other

important cardiac lesions in a population with no coronary disease reduces the specificity of the test being evaluated. Again, both the criteria by which normality is defined and the method of image interpretation will further influence specificity. When visual analysis has been used the criterion for an abnormal region has been a reduction of between 15%³ and 50%^{4,7} of peak myocardial activity; while in many studies no criteria were defined.^{5,13,19} Francisco *et al* were able to improve their specificity of 67% obtained with a computer enhanced visual or tomographic analysis to 96% by the use of a quantitative tomographic method.¹³ In the present study the criterion for abnormality of a relative reduction in thallium-201 activity of at least 25% as assessed by computer assisted visual analysis was associated with an 80% inter-observer agreement and with high values for both sensitivity and specificity. This criterion is therefore recommended for the routine interpretation of dipyridamole-exercise images.

IMPORTANCE OF THE ELECTROCARDIOGRAM
Proper assessment of the result of a dipyridamole-exercise test should include analysis of both the scintigram and the exercise electrocardiogram.² Comparison of the electrocardiogram recorded during dipyridamole-exercise or exercise testing (section 1) showed that in the presence of dipyridamole an identical average amount of ischaemic ST segment depression occurred but at a significantly lower maximal heart rate. In three patients ischaemic ST depression was seen only in the presence of dipyridamole, and this increased the sensitivity of the electrocardiogram from 76% to 84%. Others have assessed the diagnostic value of electrocardiographic changes produced by the infusion of dipyridamole, and they obtained low values for sensitivity and specificity.^{31,32} If in the present study, however, an abnormal dipyridamole-exercise test result is defined as either an ischaemic ST segment response or an abnormal scintigram the sensitivity in all 57 patients with coronary disease in section 2 rises from 87% to 96%, while the predictive accuracy of a negative result (that is no scintigraphic or electrocardiographic abnormality) increases from 76% to 92%. In those two patients with coronary disease in whom no electrocardiographic or scintigraphic abnormalities were observed the maximal heart rate was less than the 85% of predicted maximal rate required for a truly negative exercise test. Thus no patient with coronary disease could be said to have had a completely negative dipyridamole-exercise test.

DIAGNOSTIC VALUE OF REDISTRIBUTION
Redistribution of thallium-201 into regions showing

defects in early images is due primarily to delayed washout of thallium-201 from ischaemic myocardium.³³ The absence of redistribution four to six hours after injection is most often due to the presence of a myocardial scar³⁴ but may be seen in an area of viable myocardium whose blood supply is severely compromised. In such instances redistribution may be delayed until 18–24 hours.³⁵ Although in earlier studies the diagnostic value of redistribution was not emphasised data from these studies³⁵ did suggest that “reversible” defects, that is those associated with redistribution, may be more specific indicators of coronary disease than “irreversible” defects. In the present study redistribution was seen in a greater percentage of defects detected after dipyridamole-exercise testing than in those detected after exercise alone. Moreover, all 70 reversible defects produced by dipyridamole-exercise testing were in patients with important coronary disease (predictive value = 100%), whereas three of 29 irreversible defects were in patients with no coronary disease (predictive value = 89%). Since the proper selection of patients for dipyridamole-exercise imaging excludes patients with previous myocardial infarction or easily induced ischaemia during exercise or both, a “defect” seen after dipyridamole-exercise testing which shows no redistribution should thus be interpreted with caution.

Only one patient had an abnormal scintigram on exercise testing but not on dipyridamole-exercise testing. This patient's oxygen consumption and the severity of myocardial ischaemia, as judged by maximal heart rate and ST segment depression recorded during exercise, were virtually identical on both occasions. Coronary arteriography showed a single 90% stenosis of the mid-left anterior descending coronary artery and exercise imaging demonstrated (on one projection only) an inferior defect which at four hours showed no redistribution. Since there is a fairly precise correlation between the site of scintigraphic abnormalities and the location of coronary stenosis in patients with single vessel disease,³⁶ both the location and the absence of redistribution cast some doubt on the importance of this defect. In contrast in those four patients in whom only dipyridamole-exercise imaging was abnormal and in whom arteriography was performed, all defects were appropriately situated and demonstrated redistribution.

The safety and low complication rate of this technique, in which two potent stresses are being imposed together on the myocardium, depend on careful patient selection—that is the exclusion of patients with easily induced myocardial ischaemia. There have been no serious complications in the 214 patients who have undergone dipyridamole-exercise

thallium-201 imaging. Three per cent of patients had side effects of dipyridamole requiring reversal by aminophylline. These were prolonged angina (two patients), severe headache (two patients), and vomiting (one patient). In only three patients has the exercise phase not been possible.

Patients with coronary disease who have myocardial ischaemia within the first stage of the Bruce protocol have severe disease and a relatively poor prognosis.^{29,37} Unlike patients with symptoms suggestive of ischaemic heart disease but in whom the exercise electrocardiogram is negative or equivocal, diagnosis is not difficult in such patients and they do not require thallium-201 imaging.

Dipyridamole-exercise testing appears to be better than standard exercise testing in terms of sensitivity and quality of thallium-201 imaging. In patients selected on the basis of an inconclusive exercise electrocardiogram the technique is safe, effective, and very simple.

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